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Pulmonary Toxicity of Antineoplastic Agents

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Pulmonary parenchymal or pleural reactions to chemotherapeutic agents used in the management of patients with malignant diseases are being recognized with increasing frequency. Alkylating agents, asparaginase, bleomycin, methotrexate and procarbazine have all been implicated. Some of the reactions, such as the rare procarbazine pleuritis and pneumonitis, represent hypersensitivity phenomena. Others, such as alkylating agent pulmonary toxicity, appear to be direct toxic effects of the drugs. The severity of the toxicity is variable. The appearance of these pulmonary changes must be differentiated from tumor progression or a variety of possible infections. The awareness of possible pulmonary toxicity is of great importance since early discontinuation of the agent following the first hint of pulmonary toxicity may allow partial or complete reversal of the process. Continued therapy in the face of drug-related pulmonary toxicity may enhance the likelihood of irreversible pulmonary compromise with respiratory failure and death.

NEW PULMONARY INFILTRATES, pleural effusions or mediastinal masses appearing in patients with cancer are of obvious importance. Especially during aggressive antitumor chemotherapy, appropriate diagnostic studies must be done and indicated therapy instituted with all deliberate speed, since several potentially responsible pulmonary processes may be rapidly life threatening. Pulmonary infection in such immunosuppressed and often granulocytopenic patients is of primary concern. Other frequently considered possibilities include pulmonary hemorrhage associated with thrombocytopenia, and single or multiple pulmonary emboli. The appearance of recurrent or progressive malignant disease is always kept in mind. In addition to these diagnoses, another possibility not to be overlooked, even in the face of acute and severe respiratory compromise, is a pulmonary reaction to one of the therapeutic agents used in the management of these patients.

In an extensive review of drug induced pulmonary disease, Rosenow[1] compiled a long list of diagnostic and therapeutic agents capable of inducing various types of pulmonary reactions. The list is impressive in its length and diversity. Several of the agents fall directly into the armamentarium of the oncologist.

Pulmonary Reactions After Antitumor Chemotherapy

Drug-induced pulmonary reactions may be broadly divided into allergic or hypersensitivity reactions on one side and direct toxic reactions on the other (see Table 1). Allergic phenomena

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ABBREVIATIONS USED IN TEXT

ALGB = Acute Leukemia Group B
ALL = acute lymphocytic leukemia
MOPP = mechlorethamine, vincristine (Oncovin®), procarbazine and prednisone

are recognized as occurring in a small percentage of patients receiving any drug. They are not dose dependent and are not a response to any specific pharmacologic action of the offending agent. Such hypersensitivity phenomena require an induction period before an initial allergic response, but full-blown recall evolves rapidly on reexposure to small amounts of the offending agent. Reactions often include a constellation of findings such as skin rash, urticaria, bronchospasm and serum sickness. Toxic reactions—true side effects of therapy—are most often tied directly to some desired pharmacologic action of the drug. These are usually dose dependent and can be produced in a substantial percentage of patients if a sufficient amount of the agent is given. Reexposure to small quantities of the drug will not lead to the rapid reappearance of all the toxic symptoms.[2]

Hypersensitivity Reactions

True allergic reactions are seen with asparaginase and procarbazine. L-asparaginase is most frequently used in the treatment of acute lymphocytic leukemia. A review of the early National Cancer Institute experience with repetitive doses of Escherichia coli asparaginase showed a 33 percent (9/27) incidence of hives and dyspnea in children receiving the drug.[3] Treatment with antihistamines (intravenously given benadryl) and steroids usually controlled the symptoms. Further E. coli asparaginase was withheld. More recently, a switch to Erwinia asparaginase (Porton) following a reaction to the E. coli material has allowed continued asparaginase therapy without another immediate allergic reaction.

The experience with asparaginase at Memorial Hospital for Cancer and Allied Disease was reviewed in 1970.[4] Pretherapy testing with intradermal asparaginase produced an immediate wheal and flare reaction in only one case. All other reactions occurred after at least several days of daily intravenous administration. Shortness of breath occurred in 22 percent of patients. X-ray studies of the chest in these patients were not commented upon. Other manifestations of hypersensitivity included urticaria (65 percent), hypotension (18 percent) and facial edema (11 percent). In their experience, control of symptoms with antihistamines allowed continued administration of the drug.

TABLE 1.—*Chemotherapeutic Agents Causing Pulmonary Reactions*

Drugs	*Mechanism of Reaction*
L-Asparaginase	Hypersensitivity
Procarbazine	Hypersensitivity
? Azathioprine	Hypersensitivity
Methotrexate	Uncertain
Bleomycin	Direct Pulmonary Toxicity
Busulfan	Direct Pulmonary Toxicity
Chlorambucil	Direct Pulmonary Toxicity
Cyclophosphamide	Direct Pulmonary Toxicity
Melphalan	Direct Pulmonary Toxicity

Procarbazine, a monoamine oxidase inhibitor, is an important drug in therapy of Hodgkin disease. It is also used for treatment of small cell carcinomas of the lung, non-Hodgkin lymphoma and central nervous system malignancies. Allergic reactions occur with procarbazine therapy. A pleuropulmonary component to procarbazine allergy was first described by Jones and co-workers in 1972.[5] In Jones' patient, a man with Hodgkin disease receiving MOPP (a combination of mechlorethamine, vincristine [Oncovin®], procarbazine and prednisone) chemotherapy, cough, fever and shortness of breath developed, along with pulmonary infiltrates and a pleural effusion on reexposure to procarbazine during his second and third cycles of MOPP. A challenge dose of procarbazine administered under controlled conditions also evoked the entire complex of respiratory signs and symptoms, thereby confirming the suspected diagnosis of procarbazine hypersensitivity.

Another case of hypersensitivity pneumonitis during combination chemotherapy including procarbazine has been reported.[6] In this patient open lung biopsy was done which showed a proliferative alveolar reaction including interstitial leukocyte infiltration, occasional eosinophils and alveolar septal edema. No fibrosis was present and the findings were compatible with an acute allergic pneumonitis. The patient recovered fully when administration of the drugs was discontinued. In light of Jones' case report, procarbazine was quite possibly responsible for this allergic process.

Imuran® (azathioprine) has also been implicated in one case report as a cause of allergic

pneumonitis. The patient had received six weeks of orally given Imuran and bilateral basilar shadows developed on x-ray studies of the chest, in addition to clinical respiratory distress. A pronounced decrease in forced expiratory volume and forced vital capacity was shown on pulmonary function testing. This syndrome was felt to be an allergic alveolitis secondary to Imuran administration.[7] The Imuran administration was discontinued and steroids were given (prednisone, 30 mg per day). The patient improved rapidly. After three months, findings on repeat x-ray study of the chest and pulmonary function studies had returned to within normal limits. Though possible, the causal role of Imuran therapy in this situation remains speculative.

Reactions of Uncertain Mechanism

Not yet clearly defined mechanistically as hypersensitivity phenomena or toxic side effects are the pulmonary reactions associated with intermittent methotrexate administration. In 1969, Acute Leukemia Group B (ALGB) reported follow-up on 93 patients with acute lymphocytic leukemia (ALL) in whom remission induction with vincristine and prednisone had been carried out followed by maintenance therapy with biweekly administration of methotrexate (30 mg per M^2) given either orally or intramuscularly.[8] During the maintenance phase, pulmonary infiltrates that lasted up to several weeks developed in 38 of the 93 patients. Three pulmonary-related deaths occurred. One was documented as a pneumocystitis pneumonia, but the other two were undiagnosed. The startling frequency of pulmonary reactions was completely unexplained, but the authors speculated that the lung changes were most likely infectious, with the high attack rate caused by either decreased intrinsic lung clearing capacity or altered immune status induced by the methotrexate.

Within six months of the ALGB results, Clarysee and associates[9] reported on seven consecutive patients with ALL in remission given methotrexate biweekly as maintenance therapy. In each patient there developed a severe respiratory illness, characterized by fever, nonproductive cough, dyspnea and cyanosis, that appeared 12 to 100 days after initiation of biweekly administration of methotrexate. X-ray studies of the chest in each case showed bilateral interstitial pulmonary infiltrates, more pronounced in the lower lobes. No pleural effusions were noted. Moderate eosinophilia was present in five of the seven patients. In five of the seven, methotrexate therapy was continued during the respiratory illness; in the sixth it was delayed for one week; in the seventh it was discontinued. Regardless of the handling of the methotrexate therapy, the course appeared to be essentially the same. The acute illness lasted ten to 40 days, followed by a period of rapid improvement. Complete clearing of symptoms and x-ray findings occurred in all but one patient.

In Clarysee's series,[9] open lung biopsy was done in one patient. Findings included a mixed inflammatory reaction within alveolar spaces and interstitial tissue. Multinucleate giant cells and noncaseating granulomas were present. The overall appearance was similar to the histologic appearance of lung biopsy material seen in syndromes of farmer's lung or pigeon-breeder's disease. Subsequently other cases with similar histology have been reported.[10,11]

In 1972 Whitcomb and co-workers[12] reviewed the literature on methotrexate pneumonitis and were able to add an additional six patients[10,13-15] to those described by Clarysee. These new reports included patients with underlying diseases other than acute leukemia. In each case methotrexate was given either weekly or biweekly for 12 to 196 days before the appearance of the respiratory illness. In contrast to the original seven patients of Clarysee,[9] five of these new patients received steroids (30 to 120 mg of prednisone per day) for the pneumonitis. In the steroid-treated patients, defervescence seemed to be more prompt, ranging from four to eight days rather than ten to 40 days, despite apparently equivalent initial clinical and radiographic presentations. In one of the steroid-treated patients, findings that had completely cleared at treatment with 30 mg per day of prednisone reappeared when the dosage was dropped to 10 mg per day on the fourth day of steroid therapy.[14] In that patient, administration of all medication, including steroids, was discontinued when the symptoms and chest findings recurred, and the patient's condition slowly improved over the subsequent ten days.

Recently, Sostman and associates[16] updated the status of methotrexate pneumonitis with a report of 36 cases. The findings were the same as in the earlier reports of Clarysee[9] and Whitcomb[12] except that Sostman found two patients with associated pleural effusions and three with hilar adenopathy. Findings from biopsy studies done in

several patients were similar to those in Clarysee's series except that in one patient frank pulmonary fibrosis was found.

Most patients in whom methotrexate pneumonitis develops have been receiving orally given methotrexate, but this complication has also been reported for intramuscular and intravenous administration as well. In addition, Gutin and associates[17] reported the case of a patient who was receiving methotrexate intrathecally every other day for meningeal carcinomatosis of breast origin; fever, cough and pulmonary infiltrates developed after ten doses of intrathecally given methotrexate over about three and a half weeks. Peripheral count suppression without marrow involvement with tumor was seen. Measurable levels of methotrexate were found in specimens of serum one to two days after an intrathecal dose. Postmortem evaluation of the lungs showed a pattern of interstitial pneumonitis with multinucleate giant cells suggesting methotrexate lung disease.

The cause of methotrexate lung disease remains uncertain. The popular notions of direct pulmonary toxicity or hypersensitivity phenomena do not explain the common findings that continuation of methotrexate therapy during the acute illness fails to perpetuate or worsen the condition and that reexposure to methotrexate is rarely associated with reappearance of pneumonitis. Sostman[16] has suggested that the timing of drug administration appears to affect the frequency of pulmonary reactions with more frequent doses resulting in a higher rate of pulmonary toxicity.

Toxic Side Effects

As opposed to the allergic reactions discussed earlier, more characteristic toxic reactions underlie the pulmonary disease induced by busulfan, cyclophosphamide, bleomycin, chlorambucil and melphalan.

In 1961, Oliner and co-workers[18] reported two patients with chronic myelogenous leukemia treated for 9 and 13 months respectively with busulfan (Myleran®) given daily. Following this therapy, each presented with the subacute appearance of cough, fever, shortness of breath, weakness and weight loss. Physical examinations showed diffuse rales, and x-ray films of the chest showed bilateral diffuse infiltrate.[5] Lung biopsy studies showed focal chronic interstitial pneumonitis and interstitial fibrosis. An atypical proliferative appearance of the cells lining the terminal bronchioles and alveolar septae was noted. Steroids provided symptomatic benefit in both patients, but the changes shown on x-ray studies regressed only in the patient who had the nine months of therapy. Many months later, this patient again received busulfan each day. Cough, fever and respiratory distress did not reappear.

By 1966 ten cases of busulfan pulmonary toxicity—so-called "busulfan lung"—had been reported.[18-21] Several more have been reported since.[22-26] Seven of the first ten patients had been treated with orally given busulfan each day for 9 to 30 months before respiratory complaints developed. The other three had received the drug intermittently over the preceding five to eight years. In each case the patients presented with combination of fever, chills, cough, weakness, weight loss and shortness of breath. Pulmonary infiltrates were noted on x-ray studies, and restrictive defects could be shown on pulmonary function testing. This clinical constellation is sufficient to support a diagnosis of "busulfan lung." Recently, Byrnes and associates[27] have shown that the clinical impression of "busulfan lung" can be confirmed by obtaining diagnostic pulmonary tissue through a transbronchial biopsy.

The true incidence of "busulfan lung" is unknown. In a study of 40 consecutive patients, treated daily with busulfan for a median duration of 19 months, who were examined at postmortem, in only one case were there clear-cut changes of busulfan pulmonary toxicity. That patient had been severely symptomatic following 30 months of busulfan therapy.[24]

A few reports[28,29] of lung toxicity following prolonged cyclophosphamide (Cytoxan®) therapy have also appeared. One[28] involved a 23-year-old woman with Hodgkin disease who received 50 to 150 mg of cyclophosphamide orally each day for 27 months. The reports of cyclophosphamide lung disease are very reminiscent clinically, radiographically and histologically of "busulfan lung," and a similar mechanism has been proposed.

Yet another alkylating agent, chlorambucil (Leukeran®), has also been associated with fibrotic pulmonary disease. In a brief letter in the *New England Journal of Medicine,* Rubio[30] reported the cases of four patients receiving long-term therapy with chlorambucil, duration and total doses unspecified, who died with severe interstitial pulmonary fibrosis. In one of the cases the syndrome of respiratory insufficiency was

said to evolve rather acutely. The possible use of steroids in these patients was not discussed.

Of the remaining polyfunctional alkylating agents, nitrogen mustard has not been implicated in the production of pulmonary fibrosis. However, the possible association of melphalan (L-phenylalanine mustard) and pulmonary fibrosis was reported by Codling and Chakera in 1972.[31] Recently a probable case of pulmonary fibrosis associated with melphalan treatment of multiple myeloma has been reported.[32]

Bleomycin (Blenoxane®) has gained wide acceptance as an antitumor agent because of a significant antitumor effect combined with minimal myelosuppression. The drug is concentrated in skin and lung, and these two tissues have been the major sites of bleomycin toxicity. The true frequency of clinical bleomycin pulmonary toxcity and dose-schedule or time dependent aspects to toxicity remain uncertain. Japanese investigators reporting on 462 patients[33] treated with bleomycin noted a 4.2 percent incidence of pulmonary fibrosis and a 1.5 percent incidence of respiratory failure. A European cooperative study[34] reported a 3.3 percent incidence of pulmonary complications. Rudders[35] reviewed the cases of 39 patients with lymphoma treated with bleomycin. Of Rudders' patients, acute fatal respiratory failure developed in one after 210 mg of drug was given. In three others, pulmonary infiltrates appeared during bleomycin therapy and administration of the drug was discontinued. The overall incidence of pulmonary injury attributed to bleomycin was 10.4 percent.

Findings from an extensive review of the pulmonary toxicity of bleomycin by DeLena[36] and colleagues suggested a much higher rate of objective bleomycin lung toxicity. They reported a 38.9 percent incidence of this complication, defined as either the appearance of rales, ronchi or pleural rubs in patients receiving the drug (without findings of congestive heart failure or progressive tumor) or the development of pulmonary infiltrates seen on x-ray studies in the absence of clinical findings on chest examination. Whenever any signs of lung toxicity appeared, the bleomycin therapy was discontinued and antibiotics and steroids were given. In about half the patients (46 percent) in whom early lung toxicity was noted on physical examination, the physical findings regressed over one to two months after stopping bleomycin therapy. Abnormalities on x-ray studies did not develop in this group. In the other half (54 percent), early radiographic evidence of interstitial abnormalities developed within two weeks of first recognition of changes on physical examination despite immediate discontinuation of therapy with the drug. These findings did in most instances regress with time.

Dose dependence of bleomycin pulmonary toxicity has been examined extensively. Blum and co-workers[37] analyzed the cases of 808 patients from several different studies and found risk of pulmonary toxicity to increase rapidly above a total dose of 450 mg. However, characteristic lung toxicity has been seen at all dose levels, even below total doses of 50 mg in some situations.[37] The four cases of bleomycin toxicity in Rudders' series involved total doses between 210 and 300 mg.[35] DeLena and associates[36] noted 33 percent and 48 percent incidence of pulmonary toxicity in two separate series with mean toxic doses of 132 and 135 mg per M^2 respectively. They suggested frequent careful physical examinations to detect early toxicity in all patients receiving greater than 100 mg per M^2 total dose of bleomycin. Schedule dependent pulmonary toxicity (that is, high dose intermittent versus low dose daily versus infusion) has not yet been clearly shown in the literature, but DeLena has suggested that high single doses or prolonged daily administration is particularly hazardous. No change in frequency of pulmonary toxicity with ages up to 70 years old was noted by Blum[37] or Haas.[38]

The response of the pulmonary parenchyma to a wide variety of toxic insults appears to move in a fairly stereotyped progression. It is possible to show both an alveolar and an interstitial component. Reactions to alkylating agents and bleomycin conform to this model. Alveolar air spaces are lined by type I (membranous) and type II (granular) pneumocytes. These latter cells normally produce surfactant. They contain characteristic "lamellar bodies" and are easily recognized on light or electron microscopy. In response to toxic pulmonary insults, there is a decrease in number of the type I pneumocytes and hyperplasia with metaplasia of the type II cells. With continued noxious stimulation, many type II cells are shed into the intraalveolar spaces. These cells disintegrate, inducing a serofibrinous reaction, and intraalveolar material accumulates in a fashion similar to pulmonary alveolar proteinosis. Interstitial edema develops, and reticulin and mature collagen deposition takes place in the alveo-

lar septae. In time the organized alveolar masses are incorporated into the thickened alveolar walls producing extensive fibrosis.[28,39-42]

The sequential nature of this process may explain the variable response to steroid therapy. The condition of those patients treated early during the exudative phase may improve with steroid therapy[18] plus discontinuation of the offending agent. When further organization has occurred, the process is essentially irreversible, and progressive respiratory insufficiency with restrictive ventilatory defects are the rule despite steroid use.

In nearly all the toxic reactions discussed thus far, the drug implicated in the pulmonary process has been used either alone or in combination with other chemotherapeutic agents not known to produce lung disease (for example, MOPP). Several new protocol studies combine alkylator therapy with methotrexate or bleomycin, or both. The question of whether or not significantly increased incidence of pulmonary toxicity will follow from such combinations has not yet been answered. However, a recent paper by Stutz and co-workers[43] concerning a five drug regimen for breast carcinoma suggests that some increase in pulmonary toxicity may occur with such combinations. This paper reviewed the courses of 17 patients with breast cancer treated with combination chemotherapy that included Cytoxan and methotrexate. In six, noninfectious pulmonary complications developed thought to be drug related based on timing, appearance and response to steroids. The 35 percent incidence was alarmingly high, and the authors speculated on the role of combined Cytoxan and methotrexate administration as an explanation for the high rate of pulmonary complication.

Recent experience of Einhorn and associates[44] suggests that the combination of bleomycin with radiotherapy may cause an acceleration of the fibrotic pulmonary reaction seen with either agent used alone. They treated 13 patients with oat cell carcinoma using combination chemotherapy including bleomycin, adriamycin, cyclophosphamide and vincristine, as well as 4,000 rads midplane tumor dose given in ten treatment fractions (five treatments, days 22 through 26 and five treatments, days 43 through 47) to the primary lung tumor. In five patients biopsy proven generalized interstitial pulmonary fibrosis developed. This appeared within two to six weeks of completion of the bleomycin therapy, which consisted of a total of 90 mg of drug given as 15 mg intravenously each week for six doses. The pulmonary injury was widespread and severe with three patients dying of respiratory failure and the two others limited by serious respiratory insufficiency. This frequency of major pulmonary fibrosis, especially after only 90 mg of bleomycin, is alarmingly high and appears to represent a serious synergistic toxicity of bleomycin and concommitant pulmonary parenchymal irradiation. Since this synergistic toxicity was recognized, an additional group of 20 patients has been treated by Einhorn and co-workers using the same treatment protocol except for the elimination of bleomycin. No further cases of generalized fibrosis have been noted.

Summary

The pulmonary parenchyma and pleural spaces are often sites of involvement with malignant disease. In addition, opportunistic infections often present as rapidly progressive pneumonitis in patients with malignant disease. Aggressive diagnostic maneuvers to differentiate these two categories of disease are appropriate. Several antitumor agents may cause pulmonary disease as well and such reactions must be considered in the differential diagnosis of progressive pulmonary infiltrates in patients with cancer in whom chemotherapy is being carried out. Many of these toxic or hypersensitivity reactions may seriously compromise the patients' clinical status. Long-term morbidity or mortality may result. Early intervention with steroid therapy appears to have a role in control of some of these reactions. Prospective awareness of such potential toxicities may help to avoid or minimize the severity of the pulmonary injury.

Addendum

Since submission of this manuscript, Holoye and co-workers[45] have reported the case of a patient treated with long-term intermittent BCNU therapy (treatment with nitrosoureas) for more than three years in whom there developed a syndrome of dry cough, dyspnea on exertion, and mild hypoxemia (Po_2 on room air). Lung tissue showed alveolar septal thickening with fibrous connective tissue and no inflammatory reaction. There was hyperplasia of type II alveolar lining cells. Patients are rarely treated with nitrosoureas over such a prolonged period of time. However, based on this report, it appears that long-term

intermittent nitrosourea therapy may be associated with lung toxicity in the form of pulmonary fibrosis. Since nitrosoureas are thought to act through an alkylating mechanism, the potential for nitrosoureas to produce such lung toxicity should not be completely unexpected.

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